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Minutes

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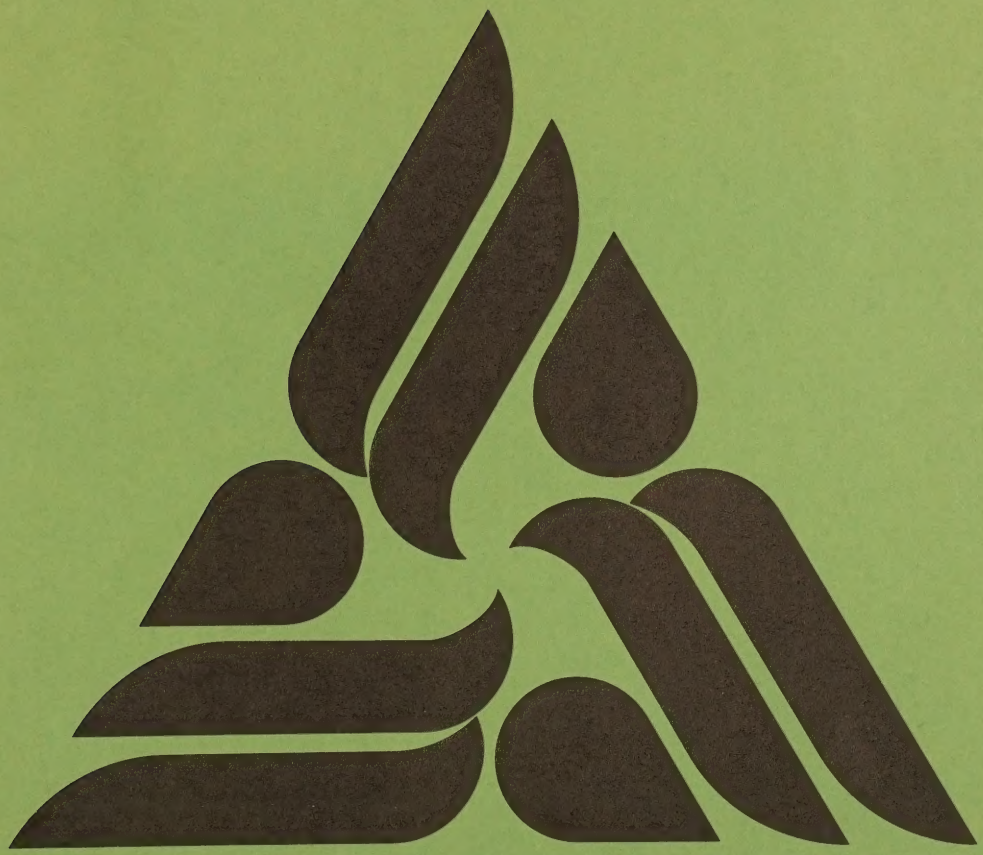
Research Guidelines Working Group

February 27-28, 1990



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UNITED STATES DEPARTMENT OF AGRICULTURE

AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE

RESEARCH GUIDELINES WORKING GROUP

MINUTES OF MEETING

February 27-28, 1990

The Research Guidelines Working Group (henceforth referred to as the Working Group) of the Agricultural Biotechnology Research Advisory Committee (ABRAC) was called to order by Dr. Sue Tolin, Chairperson, at 9:00 a.m. ABRAC members in attendance were: Dr. Tolin, Dr. Anne Vidaver, Dr. F. William Whitmore, Dr. Harold Hafs, Dr. John Kemp, and Dr. Edward Korwek. Office of Agricultural Biotechnology (OAB) staff in attendance were: Mr. Paul Stern, Ms. Maryln Cordle, Dr. Phillip O'Berry, Dr. John Gerber, and Ms. Martha Steinbock. Guests present were: Dr. Charles E. Hess; Assistant Secretary, Science and Education; Dr. Nelson Wivel, National Institutes of Health; Dr. David R. MacKenzie, National Biological Impact Assessment Program, USDA, Cooperative State Research Service (CSRS); Ralph Metzger, Ohio State University; Jo Randall, Garst Seed Company; Frank Bass, Bureau of National Affairs; Keith Berton, American Chemical Society; Dr. John Payne, USDA, APHIS; and Dr. Richard Parry, USDA, ARS.

APPROVAL OF AGENDA AND INTRODUCTORY REMARKS

Dr. Tolin announced that there were several additions to the agenda. Dr. Nelson Wivel from the National Institutes of Health (NIH) would brief the Working Group on the issue of overlap with NIH Guidelines at 9:45 a.m. Dr. Charles E. Hess, Assistant Secretary, Science and Education, would discuss the issue of scope of oversight at 10:15 a.m. Dr. Richard Parry, Agricultural Research Service (ARS), would report to the Working Group on Classification of Organisms at 11:00 a.m. With these additions, the agenda was approved.

Dr. Tolin proposed that the Working Group use the first day to go through the entire USDA Guidelines for Research With Genetically Modified Organisms Outside Contained Facilities (henceforth referred to as the Guidelines) in concept, targeting areas for revision and then go over these areas in detail the second day. The February 1, 1990 draft of the Guidelines, which had been sent to the Working Group members by Mr. Stern, would be the starting Document (No. 119) for the revisions. The goal would be to have a reasonably complete and acceptable document for submission to the ABRAC by the close of the meeting. The Working Group agreed to this approach.

Overview of the Guidelines

Mr. Paul Stern briefed the Working Group on the February 1, 1990 draft of the Guidelines. He said that although there were many details that could be worked on after the Guidelines were published for public comment, he believed that the current document was a good one and was close to being ready for publication. He also said that he had attempted to soften the language in the current draft and avoided using absolute terms which would be difficult to defend scientifically. Referring to the use of the term "contained facility", he said that the Working Group needed to see how the Guidelines would fit with the NIH Guidelines, but that ABRAC should not compromise its principles by trying to conform to NIH. He said some questions remained about the section on conflict of interest, and that it had proven to be difficult to define "direct financial interest." He noted that he had also rewritten Section XI on the documentation to be submitted by the Principal Investigator (PI), and had sent it to the chair of the Working Group.

Dr. Tolin remarked that Section XI was much improved and asked that it be distributed to others at the meeting. She suggested that the Guidelines be further revised to include six steps instead of five, making the fifth step the preparation of the summary or submission document. She stated Mr. Stern had improved the draft Guidelines throughout.

Tone of the Guidelines

Dr. Tolin opened discussion on the tone of the Guidelines. Dr. Vidaver said she liked the tone very much because much of the absoluteness is gone. However, there are a few places where changes still need to be made. She said the Guidelines should reflect what was biologically correct and avoid using absolute statements such as "assure safety."

Ms. Cordle said she believed the word "safety" means reasonable certainty of safety. Dr. Korwek said if that is the way the term is to be used in the Guidelines, then it should be explicitly defined as such. He said he was also concerned about the absolute statements in the Guidelines. He added that some of the absolutisms could be balanced by weighing risk against benefit, and that this rationale could be developed in the preamble.

Dr. Tolin pointed out that at one point the Guidelines had included a definition of safety. Dr. Korwek said it would be wise to include the definition in the current draft.

Dr. Vidaver called the Working Group's attention to the term "assure safety" in line 8, page 3 in the Purpose section. She said she would prefer the word "maximize" to assure, which she considered absolutist. Dr. Korwek suggested "optimize" might be better. Dr. Tolin asked Dr. Korwek to define "safety" for the purposes of the Guidelines and then decide which word should be used.

Dr. Vidaver then referred to several other points in the Guidelines where similar uses of the word "safety" occurred. She also mentioned softening such absolute statements as "to prevent escape," the "inability of the parent organism" and "to contain an inadvertent release."

Mr. Stern commented that some of this absolute language is used to describe a level one organism, and thus it is intended to be stringent.

Overlap of NIH and USDA Oversight

Ms. Cordle introduced Dr. Nelson Wivel, Acting Director, Office of Recombinant DNA Activities (ORDA), NIH. She said she and Dr. Wivel had discussed the issue of overlapping oversight and that USDA and NIH legal staffs had also discussed the issue. She said NIH/ORDA was planning a series of meetings to discuss its future role. She said, in the short-term, the overlap question involves appendix Q of the NIH Guidelines[1], especially with regard to recombinant DNA containing whole animal studies at the BL1-N level. She said several other questions need to be addressed, including whether USDA wishes to have oversight over all outdoor research and if USDA wishes to cover contained research which does not meet the NIH Guidelines.

Dr. Korwek said if the research is contained, such an action is in the purview of NIH and covered under its Guidelines. Dr. Wivel responded that the NIH Guidelines had been amended in 1987 to allow an equivalent review by another government agency, so that it might be better for USDA to handle some types of reviews that can now be done by NIH under its Guidelines.

Dr. Tolin asked if a change in the NIH Guidelines in the recommended containment for a particular type of research would require a review of the NIH Recombinant DNA Advisory Committee (RAC). Dr. Wivel said that any amendment of the NIH Guidelines requires review by the RAC and approval of the Director of NIH, but an amendment was made in 1987 that allows equivalent review by another government agency with appropriate jurisdiction in lieu of NIH action.

Ms. Cordle said that in some cases she would find it difficult to draw the line between containment and confinement, for example, in a greenhouse without screens.

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[1] Appendices P and Q refer to proposed revisions to the NIH Guidelines which were published in the August 11, 1987 Federal Register, then revised and approved by the RAC at a subsequent meeting. Revision of the NIH Guidelines includes these appendices, and inclusion of references to them in Section III awaits NIH approval.

Dr. Kemp and Dr. Korwek, however, agreed that it was possible to draw the line between containment and confinement and that contained research should be conducted as described in the NIH Guidelines.

Dr. Hafs asked if there is concern about oversight of agricultural research versus other types of research. Dr. Wivel replied that it wasn't so much concern, but that once the ABRAC Guidelines are in place, NIH could be flexible and some types of oversight could be taken over by USDA because the NIH Guidelines allow for comparable review.

Ms. Cordle stated that in the USDA Guidelines "contained facility" refers to a structure with walls, roof and floor, such as a laboratory or a greenhouse. But, she questioned, are animals in a barn contained or confined? Dr. Tolin responded that Appendix Q describes various types of barns and how practices, as well as facilities, may determine which it is.

Dr. Korwek said it seemed possible to have concurrent jurisdiction, so that a PI could come to either USDA or NIH. Dr. Kemp agreed, saying the researcher could have two routes, either using NIH to change the containment or coming to USDA as an experiment to be confined.

Dr. David MacKenzie, Cooperative State Research Service (CSRS), said that there should be clarity in jurisdiction, so as not to confuse the scientific community. He added that in the case of the Auburn experiment with transgenic fish, NIH had different standards than USDA.

Dr. Hafs said he believed it is appropriate to give the researcher some flexibility. Dr. Wivel said if NIH received an application for review which would likely be only for deliberate release experiments, they believed should go to ABRAC, then they would immediately direct the researcher to USDA. There would not be a long delay.

Ms. Cordle stated she interprets the current language in the USDA Guidelines as meaning that if an experiment does not meet NIH requirements, then it is considered a planned introduction into the environment. Dr. Vidaver agreed, but said the BL1-N level of Appendix Q does not agree with this interpretation because Appendix Q covers research outside a confined facility.

Dr. Korwek said there are two responses to the problem. One is put an exception in the USDA Guidelines for this level of Appendix Q, and the other is to bring experiments described for level 1 of Appendix Q under USDA oversight.

Dr. Vidaver asked if NIH would consider letting ABRAC take over Appendix Q, Level 1. Dr. Wivel responded that functionally it could be done.

Dr. Tolin said ABRAC needed to consider Appendix Q, Level 1, to see if it is compatible with the Guidelines. Dr. Wivel agreed.

Ms. Cordle said that at the moment it seemed the best way to proceed was to leave flexibility for the researcher to go either to ABRAC or NIH. The Working Group reached consensus on this point.

Dr. Tolin referred to the language in the USDA Guidelines (Section II-A-2 and Section III-A, l. 8-13, p.6) "that meets the NIH Guidelines." She said that "described in the NIH Guidelines" should be substituted because the NIH USDA Guidelines do not require anything and that they do describe containment facilities and practices. She said the current wording mixes descriptions with actions.

Dr. Vidaver suggested that a footnote in the USDA Guidelines should define "contained facility" as in the NIH Guidelines. Dr. Tolin added that as an alternative the entire Appendices P and Q might be published as appendices to the USDA Guidelines. Dr. Vidaver said that might present problems because of inconsistencies.

Dr. Kemp asked the Working Group to consider the wording in Section III-A, which states "research involving rDNA molecules conducted within contained facilities should be carried out in accordance with the NIH Guidelines." He suggested changing "should" to "must." Ms. Cordle and Ms. Steinbock said that this contradicted the Working Group's earlier decision to allow researchers to come to ABRAC for experiments which do not meet the NIH Guidelines.

Dr. Korwek noted that this language was trying to address a number of different issues. He agreed with Ms. Cordle that the Working Group had decided on concurrent jurisdiction.

Dr. Kemp said scientists would take the path of least resistance, and that working under the USDA Guidelines to establish confinement would be easier than changing the NIH Guidelines. He added that he would like to see the same Institutional Biosafety Committees (IBCs) serve both USDA and NIH. Dr. Wivel said that most IBCs would favor that.

Ms. Cordle noted that NIH and USDA interpret deliberate release differently. She said that USDA believes if research is conducted outdoors, for example in a pond, then the National Environmental Policy Act (NEPA) applies. But NIH has said NEPA does not apply unless the investigator plans a deliberate release of the organism into the environment.

Dr. Hafs asked if it would help to better define containment and confinement. Ms. Cordle said that it would. Dr. Tolin said many hours had been spent debating the

meaning of "deliberate release." She said that ABRAC is dealing with planned introduction.

Dr. MacKenzie asked about the status of Appendix L? Dr. Wivel said it is still a part of the NIH Guidelines, and it allows for a case-by-case review by the RAC Plant Working Group of release of plants.

Dr. John Payne, Animal and Plant Health Inspection Service (APHIS), said that it is not a matter of semantics. He said it is easier to do NEPA documentation up front than to get involved in a legal action after the fact.

Dr. Tolin referred the Working Group to the language in question, the parenthetical phrase on p. 6, l. 8-13 in Section III of the USDA Guidelines, which states that contained research should be carried out in accordance with the NIH Guidelines. Dr. Korwek noted that this is an example of trying to provide guidance, but actually confusing the situation. He recommended deleting the sentence. The Working Group reached consensus on this point.

Scope of Oversight

Dr. Charles Hess updated the Working Group on the Biotechnology Science Coordinating Committee (BSCC) discussions on scope. He reported that after the comments of the ABRAC and others were considered, Option 4 was presented to the BSCC. The BSCC asked that the BSCC Subcommittee on Scope try another approach beginning with all organisms and then giving a series of exclusions. However, after studying this option the majority of the Subcommittee concluded it was flawed. Thus, he would recommend adoption of Option 4 with some new wording of the exclusions. In the interim, he said, for planning purposes the ABRAC should use the interpretation of Option 4 provided by Ms. Cordle.

Ms. Cordle stated that she had provided a discussion paper to the Working Group members which was based on Option 4, but included refinements suggested by ABRAC (Appendix A). She said she had organized the exclusions taxonomically at the suggestion of ABRAC. She said she had also drafted some specific language justifying the exclusions for the Working Group to consider. She said there is room for the Working Group to interpret some of the BSCC language.

Dr. Tolin said she envisioned having a section in the USDA Guidelines entitled, "Exemptions," but that the justification would be in the preamble. Ms. Cordle agreed that the justification would be in the preamble, and the exclusions would be in Section III which would be called "Applicability and Scope."

Ms. Cordle suggested that the Working Group begin its discussions on the first covering statement. She said the difference in covering statements between the ABRAC scope and Option 4 is how specifically deletions are described.

Dr. Tolin said she had no problem with the treatment of deletions in the discussion paper as long as manipulation is clarified in the footnote.

Dr. Hafs asked why it was important to keep deletions in the covering statement in the first place. Dr. Vidaver said it is important to recognize that deletions are a result of genetic manipulation. Dr. Tolin said deletions are significant for viruses. She said there are cases where the total genome causes a very mild reaction, and after a deletion, it causes a necrotic reaction. The Working Group reached consensus that deletions should be covered by the opening statement of the Scope section of the USDA Guidelines and explicitly mentioned as a type of genetic modification.

Dr. Kemp asked the Working Group to reconsider the original problem with scope definition. He said some techniques such as protoplast fusion were now being used to make intergeneric crosses, yet ABRAC still wishes to exempt them because of familiarity. This is difficult to justify scientifically.

Dr. Hess replied that the BSCC subcommittee had studied this issue at length. He added that the dogma of product versus process has become so locked in peoples' minds that it was difficult to get some people to recognize that information about the process is helpful in understanding the risk of the product. He said two advisory groups had failed to come up with a different approach to scope which would work as well as Option 4, and that, in his opinion, it was time to get off dead center and try and resolve the scope issue by going for public comment.

Dr. Kemp agreed it was time to take action; however, he proposed that the Working Group add a consideration of taxonomy to the exclusions, cutting by genera or species. He added that despite his concern, he supported Option 4 and wanted to see it published for public comment.

Ms. Cordle asked the Working Group to consider the details of the scope language. Dr. Hess agreed saying the guidance provided in Option 4 should be interpreted by ABRAC in light of the specific system of oversight it was developing.

Dr. Tolin asked the Working Group to compare the broad opening statements on scope in the current draft of the USDA Guidelines (Doc. No. 119) with that provided by Ms. Cordle (Appendix A) which is based on Option 4. Dr. Korwek said he preferred the ABRAC version because it is tighter and more to the point. He said the version in Ms. Cordle's handout creates some ambiguity, particularly with regard to including extrachromosomal DNA in the genome.

Dr. Tolin suggested that the language be amended to read "insertion, deletion or other manipulation of their genomes or other DNA or RNA." The Working Group considered this suggested amendment but did not believe it was an improvement.

Dr. Hafs asked if the word "genome" should be included in the ABRAC scope. Ms. Cordle said she believed it would make a positive contribution, but since no one else seemed to believe it important, it could be left out. The Working Group reached consensus that the word genome could be left out.

Dr. Korwek pointed out that the wording in the opening of the BSCC scope was ambiguous about whether traditional breeding is excluded up front, while the ABRAC statement explicitly mentions only organisms modified from deliberate insertion, deletion or other manipulation, and thus, clearly begins by excluding traditional breeding. Ms. Cordle said natural reproduction is excluded in both cases.

Dr. MacKenzie noted that if the ABRAC wished to exclude all traditional breeding, it could not do so on the basis of familiarity because, given the diversity of nature, scientists could not be "familiar" with every species. Dr. Hafs argued that the principles of quantitative genetics are so well established, that it is unnecessary to go back and prove them for each and every species. Dr. MacKenzie agreed, saying that all plants could be excluded on the basis that adequate oversight already exists; however, this is also a difficult argument to make.

Dr. Kemp suggested that the Working Group take a pragmatic approach and let the opening statement stand as written in the Guidelines and see what the scientific community and public say about it after it is published in the Federal Register. Dr. Whitmore agreed. The Group reached consensus to leave the opening statement of the Scope statement in the USDA Guidelines as drafted.

Dr. Tolin asked the group to look at exclusion (1) of Appendix A (page 4) which deals with plants. She asked why the BSCC Subcommittee had limited it to vascular plants. She said she had consulted Peter Raven's Biology of Plants which gives the classification of the plant kingdom. She distributed a copy of a table which gives the classification of organisms traditionally regarded as plants to the Working Group (Appendix B).

Ms. Cordle asked the Working Group if they wished to exclude traditional breeding of all plants. Dr. Korwek asked why it would be inherently more dangerous to work with bryophytes than vascular plants. Dr. Payne and Ms. Cordle noted that the justification for this exclusion is based on examples of domesticated plants. Dr. Tolin said she did not want to limit the exclusion to only domesticated plants; however, she said it might be wise to consider drawing the line at seed plants.

Dr. Korwek said that at the last meeting of the ABRAC, Dr. Lois Miller had raised the point that algae should not be excluded regardless of the techniques used. Dr. Korwek said this should be explicitly explained in a footnote.

Dr. Hafs said that, as with animals, all plants should be covered by the exclusion on the basis of familiarity with the principles of quantitative genetics. Dr. Kemp agreed.

Dr. Hafs asked the Working Group if they wished to cover embryo rescue in the exclusion for all plants? The Working Group reached consensus that all embryo rescue in plants, including cross-species embryo rescue, should be excluded from the scope of oversight. They agreed to work on a justification for the exclusion.

Dr. MacKenzie asked if "mutagenesis" in exclusion (1) includes direct mutagenesis and transposon mutagenesis? Dr. Tolin said that she believes the ABRAC intended exclusion (1) to cover chemical and physical mutagenesis in plants. The Working Group reached consensus on this point.

Dr. Vidaver asked if transposable elements would be excluded because it comes under traditional plant breeding. Dr. Tolin said that it would. Dr. MacKenzie pointed out that the words "solely from" are very important because otherwise the case where a maize transposable element is deliberately inserted into a rice plant might also be excluded from oversight.

Dr. Korwek pointed out that the National Research Council (NRC) Report, Field Testing Genetically Modified Organisms, A Framework for Decisions, (henceforth referred to as the NRC Report) started out with a broad generalization that all plants formed by these "so-called" traditional techniques would be deemed "familiar." However, the examples given were largely crop plants. He said he was unsure if genetically modified plants such as bryophytes introduced into the environment would be considered familiar.

Report on the Classification of Unmodified Organisms

Dr. Richard Parry, ARS, reported on the findings of testing the system of classifying unmodified organisms laid out in the USDA Guidelines. He said the USDA Guidelines were sent to six scientists with instructions to use them to classify organisms within the scientists' immediate field of familiarity.

Dr. Parry said the results of the test varied. Dr. Jim Cook, a plant pathologist, commended the Guidelines because they tend to formalize a longstanding, albeit informal system, used by scientists when conducting experiments. He suggested incorporating a dichotomous key into the entire classification exercise. Such a key would allow the PI to skip through to later questions if, for example, an organism were a pest or pathogen.

Dr. Tolin pointed out such an approach would correspond with the NRC Report. Dr. Parry said that Dr. Cook suggested that if an organism is a known human pathogen it should be an automatic (5) or, if an organism were unable to persist in competition with indigenous competitors it would be a (1).

Mr. Stern referred the Working Group to a statement in Section VI-B-2-a-ii of the USDA Guidelines which says, "although the parental organism may not be a pest/pathogen, it may become one through the exchange of genetic information." Dr. Vidaver disagreed in that she did not believe that all known human pathogens should automatically be classified as (5).

Dr. Parry said that Dr. Matt Greenstone, an entomologist, produced an interesting example of a hunting spider which is found widely in nature, but would be classified a (4) or (5) because of its vigorous competition in the environment. But in reality, it is considered an innocuous organism. Dr. Parry said in general the six scientists tended to err on the side of higher numbers, rather than lower.

Dr. Parry said Dr. Bill Dowler suggested a peer group or expert panel be established to assist PIs in classifying organisms. Dr. Parry noted that most of the six scientists had less trouble with the system after he discussed it with them. He said he concluded there needs to be an intense dialogue with the scientific community once the USDA Guidelines are published.

Dr. Kemp asked if the scientists commented on Table 1[2]. Dr. Parry said they had been given an earlier, unfinished version of Table 1. Dr. Kemp said he would like to have experts review the completed Table 1 because he would not want it to be published for public comment if there were glaring errors. He asked if it would be possible to give them the completed Table 1 for review?

Dr. Tolin thanked Dr. Parry for his input and pointed out that the Working Group would return to have a lengthier discussion of how to improve overail the section on classification of organisms.

Scope of Oversight

Dr. Tolin reopened the discussion on exclusion (1) of the scope of oversight proposed in Appendix A. Dr. Kemp said he believed the Working Group had decided to exclude vascular plants and bryophytes for all the techniques listed in exclusion (1). Other

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[2] Table 1 refers to a table in the minutes of the June 22-23, 1989, Guidelines Working Group, which is appended to these minutes as Appendix H.

organisms which might be classified as plants (fungi, algae, etc.) could be considered in other exclusions because, from the point of view of confinement they were more like microorganisms. The Working Group reached consensus on these points.

Dr. Tolin said the Working Group should do some editing of the justification so that it would be appropriate. She said she noted that the discussion of tissue culture needed amendment. For example, fruit crops which are produced by traditional vegetative propagation techniques should clearly be excluded. She said the exclusion could read, "plants resulting solely from traditional breeding or propagation techniques such as hand pollination, chemical or physical mutagenesis." Dr. Vidaver concurred.

Based on these suggestions Drs. Kemp and Whitmore agreed to modify exclusion (1) and report back to the Group.

Dr. Vidaver proposed that the Working Group consider exclusion (2) which deals with animals.

Dr. Hafs suggested the word "vertebrate" be deleted so that all animals would be excluded from oversight for the techniques listed.

Dr. Vidaver asked if traditional breeding would include insect manipulation.

Dr. Tolin suggested rewording the exclusion to make it parallel with exclusion (1) by adding the words, "solely from" and "for example." Dr. Vidaver agreed.

Dr. Kemp said the Working Group should keep in mind what the new exclusion would now cover, for example, nematodes. Dr. Hafs said that nematodes are animals. Dr. Tolin commented that the Working Group might find it useful to have a table classifying the animal kingdom.

Ms. Cordle said she believed the Working Group should exclude only vertebrate animals based on familiarity. The Working Group disagreed. They reached consensus that exclusion (2) should cover all animals.

Ms. Cordle said the Working Group should not use "for example." She said the Working Group should decide specifically what to include and what to exclude. She also said it was unnecessary for the words "traditional breeding techniques" to be used if the Working Group found these words difficult to work with. She noted that all exclusions had to be adequately justified. She said she was concerned about excluding traditional breeding of insects.

Dr. Whitmore said currently exclusion (2) is modifying the phrase, "traditional breeding techniques" with a lot of things which are not traditional, such as superovulation.

Dr. Tolin suggested someone take on the assignment of justifying all animals on the basis of familiarity with the parent organism. Dr. Hafs said that if each organism had to be justified, it would be an impossible task. Dr. Tolin said the question is whether any new risk assessment issues are raised.

Dr. Hafs said the principles of quantitative genetics are broadly understood, so that there is little uncertainty in traditional breeding in all animals. Dr. Kemp said much of the justification provided by the BSCC would also apply to non-vertebrate animals; however, confinement issues might be different for some animals such as insects.

Ms. Cordle said that the BSCC subcommittee believed that insects, worms and mollusks should not be excluded from oversight. She said if the ABRAC took another approach, it should provide a justification that would stand up when the USDA Guidelines worked through the Environmental Impact Statement (EIS) process.

Dr. Tolin and Dr. Vidaver noted that there are domesticated insects and mollusks, such as silkworms and pearl-bearing oysters. Dr. Hafs agreed, saying there are enough examples in all classes of animals that the broader exclusion could be justified. The Working Group reached consensus on this point.

Ms. Cordle asked the Working Group to consider if there were any techniques listed that should not be excluded for all animals. Dr. O'Berry suggested embryo splitting might be a problem in some cases.

Dr. Tolin asked Dr. O'Berry and Dr. Hafs to work on exclusion (2) and the justification and report back to the Working Group.

Dr. Tolin asked the Working Group to review exclusion (3) which deals with microorganisms. Dr. Vidaver noted that for the purposes of scope, microorganisms are being defined as viruses, bacteria, fungi, and algae. She asked if this definition shouldn't be inserted in a footnote or appendix? She noted that the public had concern about all microorganisms, regardless of class, because they are small and have certain intrinsic properties.

Dr. Vidaver recommended that the USDA Guidelines explicitly define microorganisms as organisms which are microscopic, including some insects and nematodes which are not visible to the human eye. Dr. Tolin said that because the USDA Guidelines suggest confinement level, irrespective of whether an organism is an animal, plant or microorganism, that it may be unnecessary to extend the definition of microorganism to include microscopic insects, etc.

Dr. Tolin asked why in exclusion (3) it says "the proposed definition is not intended to cover organisms that result from asexual reproduction?" She noted that all viruses

reproduce asexually. She suggested that the BSCC subcommittee take another look at this section of the exclusion.

Dr. Korwek said that he believes it will be difficult to justify exclusion 3 because he feels there is not sufficient familiarity with many microorganisms introduced into the environment. Ms. Cordle said that the exclusion had been carefully drafted by the BSCC subcommittee and that it was not justified on the same basis as exclusions (1) and (2).

Dr. Tolin asked Dr. Vidaver to work on exclusion 3 and report back to the Working Group tomorrow. She asked the entire Working Group to look at the other exclusions.

Classification of the Parental Organism

Dr. Tolin asked the Working Group to return to a discussion of the parental (unmodified) organism and classification for safety category.

Dr. Kemp said there are two separate issues to be considered. One is leading the PI through the steps more appropriately and the second is obtaining the appropriate classification of organisms. In the latter case, he stated that organisms are often classified more stringently than necessary because individuals added or averaged the numbers after each step, rather than according them unequal weights. He said he believed Table 1 helped clarify these points.

Mr. Stern suggested that assigning numbers to individual attributes is not a useful exercise. Dr. Tolin disagreed, stating that it is useful to assign numbers but they should not be averaged to obtain the overall safety category. Dr. Vidaver suggested that language be added to the USDA Guidelines to clarify this point. Dr. Tolin pointed out that in the first drafting of the original Working Group on USDA Guidelines, such language had been developed, but that it had been lost in subsequent drafts. Mr. Stern noted that the language has been moved and now appears in Section VI, page 11 of the USDA Guidelines (Doc. No. 119).

Dr. Korwek asked about the basic concern of the Working Group with this section. Dr. Hafs and Dr. O'Berry said that if PI's reached too high a number as a safety category because they misunderstood the procedure, that they might decide not to do the experiment because the costs would be too high or they did not have the proper facilities.

Dr. Korwek said he believed PI's would come to the IBC or ABRAC if they came up with numbers which seemed unreasonably high. Dr. Tolin agreed that the proposed experiment would eventually come to ABRAC which could correct the error in

classification. Dr. O'Berry said that in practice a telephone call to the IBC might suffice to correct the mistake.

Dr. Vidaver proposed that this section of the USDA Guidelines be modified, either by giving examples or by additional narrative explanation. Dr. Korwek said that examples would help, but that a general statement might be added to clarify how to proceed through the classification procedure. Dr. Kemp agreed, noting that the way this section is currently drafted implies that the PI can assign a number to each attribute and then average these numbers.

Dr. Vidaver suggested a statement such as "the end result of the process is not a summation, nor the mean, nor the highest of the numbers assigned to individual attributes. The PI is expected to use sound scientific judgment in deciding the weight of the various attributes." The Working Group reached consensus that such a statement should be added.

Dr. Tolin pointed out that the ABRAC had never come up with a process for reviewing the examples that individuals drafted and that were included in the Minutes of the Working Group on Classification and summarized in Table 1. Dr. Kemp said he had hoped ARS scientists would have examined the examples. But, as Dr. Parry reported earlier, they wrote additional ones. Dr. John Gerber said that it was important to have a classification procedure which produced consistent results, so that knowledgeable experts would come up with the same conclusion for each classification.

Dr. Tolin asked how the ABRAC should proceed to get the examples reviewed. Ms. Cordle stated that it is important to get the examples ready to go as an appendix to the USDA Guidelines. Dr. Tolin said that as a first step each original author should have an opportunity to make revisions. It was agreed the OAB should send out the examples to the authors and ask them to make revisions by a certain date.

Dr. Vidaver said that she had developed an example classification for a microorganism which had already been approved by EPA and USDA and that she had had little trouble using the procedures in the USDA Guidelines. Ms. Cordle said this could be added to the list of twelve examples.

Dr. Kemp suggested ARS be used to review the examples. Dr. Tolin and Dr. Vidaver concurred, and added that the review should go beyond ARS scientists.

Ms. Cordle said the end product should be examples which were consistent, particularly with regard to the amount of documentation provided. She noted some examples gave 20 references, while others gave one reference.

Dr. Kemp suggested that the examples go back to the original authors with a letter saying you have two weeks to make revisions, otherwise we are going to press. Ms.

Martha Steinbock suggested it might be better to select a few examples which were well done, and tell the authors, we like these, please make your example consistent with these.

Dr. Tolin pointed out that you might need more detail for a (5) than for a (1.) Dr. Korwek agreed, yet he stated that he also agreed with Ms. Cordle that there needs to be some level of consistency. Dr. Vidaver said it was important to avoid asking for too much detail which would be a burden to the PI.

Dr. Tolin asked if everyone agreed with the overall level of safety concern arrived at for each example. The Working Group did not have any particular disagreements with any assignments of levels, but several members noted it had been quite awhile since they had reviewed the classifications in detail.

Dr. O'Berry proposed that each author look over their example again, particularly with regard to the amount of documentation needed, and make any changes they believed to be necessary. The Working Group reached consensus on this point. Dr. Tolin asked OAB to contact each author and give them instructions to compare their examples to the others and make any changes desired. She asked OAB to select a few examples as models to encourage consistency.

Ms. Cordle asked if OAB should also seek additional ARS or other reviews. Dr. Vidaver agreed to ask some scientists at her institution to look over a few examples. Dr. Tolin suggested that Dr. Fred Gould and Dr. Lois Miller be asked to review the examples on insects. Dr. Vidaver asked OAB to find other reviewers as appropriate.

Dr. Kemp asked if the entire minutes of the June 22-23, 1989 Working Group on Classification of Organisms would be published with the USDA Guidelines? Ms. Cordle said it might be printed as an appendix. Dr. Tolin pointed out that since the USDA Guidelines have been redrafted, the references in the Minutes and sections of the Guidelines don't match. Thus, the minutes would have to be edited.

Dr. Tolin asked the Working Group to review Section VI-B of the USDA Guidelines, "Classification Procedure." She said she felt strongly that the words "describe and document" should be replaced by "assess." She said that she preferred a question format which seemed less imposing than "describe and document." She said she had edited this section to put statements in the form of questions.

Dr. O'Berry noted that this changed the flavor of the section and seemed to grant the PI more discretion. The "describe and document" approach requires that the PI put his/her rationale down on paper.

Dr. Kemp suggested that several of the sections of this part of the Guidelines be changed in order. He suggested that Section VI-B come first and state that Action 1 is

to describe the accessible environment. He said the concept of "safety" could be introduced in the next session. Section V-A would be moved back. Dr. Korwek agreed with this suggestion, however, he suggested the need for cross referencing. The Working Group reached consensus that the order of the sections be switched.

Dr. Kemp asked if Section VI-B, Action I (describe the accessible environment) and Action II (describe the relevant attributes of the parental organism in the accessible environment) were redundant. Dr. Hafs said they should be combined.

Dr. O'Berry disagreed, stating that one deals with the environment and the other with the interaction of the organism with the environment. Dr. Korwek said that following this logic that there should be a separate action on only the parental organism. Dr. Tolin disagreed saying it is already covered in Action II. Mr. Stern referred the Working Group to the introduction to this section which says, "in order to conduct safe research...the attributes of the organism must be evaluated within...the environment in which the research is to be performed."

Ms. Cordle said that the concept of the accessible environment needed to be clarified. Dr. Tolin said the clarification should be included in Action I and that the examples should be revised to conform to this clarification.

Dr. Tolin agreed to revise Sections V and VI, taking into consideration the suggestions of the group, and report back to the Working Group. She would consider the comments of the Working Group as well as a draft revision provided to her by Mr. Stern.

Dr. Tolin asked the Working Group to consider the five levels of safety concern for parental organisms. She said she was convinced that there needs to be five levels, but is still concerned that it is hard to differentiate between levels (2), (3), and (4). Dr. Korwek said that the full ABRAC had reviewed this and concluded that there would be some wishy-washiness, but had decided to stick with five levels.

Dr. Hafs pointed out that the earlier attempt to avoid absolutisms, that level (1) now is very close to level (2). He added that if level (1) were too stringent, that nothing would ever be classified as a level (1). Dr. Hafs said the current language for level one "virtually no adverse effects" might be the best that the Working Group could come up with. Dr. Korwek said he was comfortable with the current language.

Dr. Tolin raised the question whether "and" or "or" should connect the subsections. The Working Group reached consensus that "or" should be used.

Dr. Tolin said that the phrase "furthermore the mere existence of any one attribute will not necessarily indicate a level (1)", should be moved to the introductory portion of the section. Dr. Whitmore cautioned that in the redraft, care should be taken not to jump

into level (1) without adequately laying the groundwork. Dr. Korwek agreed with Dr. Whitmore.

Ms. Cordle asked the Working Group to consider if these were the proper attributes. The Working Group was satisfied that the attributes covered the important factors to be considered when assigning a safety category to the parental organism.

Type of Genetic Modification

Dr. Tolin asked the Working Group to consider Section VII, Type of Genetic Modification.

Dr. Korwek said the opening paragraph of this section is too long and should be divided.

Dr. Vidaver asked if, in Section VII-C-1, the phrase "insertions and/or deletions" should be amended to read "insertions, deletions and/or rearrangements that effect the expression..." Dr. Korwek asked if this change would mean that rearrangements would fall under Type (2). He said it might be necessary to add the new wording to all types of modifications to avoid this implication. Mr. Stern pointed out that each type of modification is drafted differently.

Dr. Tolin asked if in Section VII-B-2 the request for "substantial documentation" should be moved to Section XI under "Submissions." Ms. Cordle said the wording may be incorrect, but the intent is to require adequate justification for a type of modification. Dr. O'Berry suggested cross-referencing this phrase to Section XI.

Dr. Tolin asked if the Working Group would like to consider adding a type (4) modification because, as the Guidelines now stand, everything that is possibly adverse and everything that is known to be adverse is lumped together. Dr. Korwek said the full ABRAC had discussed this issue and decided against adding a fourth type of modification.

Level of Safety Concern for the Genetically Modified Organism

Ms. Cordle asked if the USDA Guidelines should contain both the levels of safety concern for the genetically modified organism as described in Table 2, (Doc. No. 119, p. 26) and a narrative description of the levels (Section VIII).

Dr. Tolin said the narrative description could be deleted, and the text could refer to Table 2. The Working Group reached consensus on this point.

Dr. Hafs asked why if a safety level were changed more than two levels, the experiment should automatically come to ABRAC. Dr. Tolin explained that it is because the consequence of a mistake is greater. Dr. Korwek said this is an important point and shouldn't be relegated to a footnote.

Dr. Hafs said he is concerned that ABRAC will end up reviewing a lot of low risk experiments. Mr. Stern said that if this does happen, it would only be in the beginning until the cases had received an initial review.

Confinement

Dr. Tolin asked the Working Group to consider Section IX on confinement. Dr. O'Berry said he had reviewed the section and believed that it is satisfactory. He said it contains all the major points contained in the NRC report and the Organization for Economic Cooperation and Development (OECD) document on Good Developmental Practices (GDP).

Dr. Hafs agreed, stating that the USDA Guidelines shouldn't go into too much detail on confinement.

Ms. Cordle suggested that the phrase "good agricultural practices" be changed to "good agricultural research practices." The Working Group agreed to this change.

Dr. Korwek suggested that the confinement levels be cross referenced to the definitions section.

Dr. Tolin noted that the confinement section should also cover such things as monitoring and security, which are covered in the generic submission form developed by the National Biological Impact Assessment Program (NBIAP). She said the confinement section of the USDA Guidelines should be considered together with the section on documentation to be submitted by the PI, to make sure they are consistent. She added that this section is judgmental, but that this is unavoidable.

Dr. Tolin observed that some people have had difficulty with linking level of review to confinement because choice of confinement level is, by necessity, subjective. The Working Group agreed to discuss this issue the next day.

Dr. Tolin asked the Working Group to consider interchanging the order of Section X and Section XI. Ms. Cordle asked the Group to consider carefully the whole issue of how the confinement section should be handled in the Guidelines.

Additional Scope of Oversight Issues

Dr. Korwek said that since he would not be attending the session the next day, he would like to raise an issue about exclusion (3) which deals with microorganisms. He said he is concerned that the exclusion is too broad and that there is no reference to the environment. He asked the Working Group to carefully consider this issue in their discussions the next day.

Dr. Korwek said he is also concerned that the issue of overlap with the NIH Guidelines has not been adequately resolved. He said changes in leadership at NIH could result in NIH being less willing to work with USDA to minimize problems resulting from overlapping jurisdiction. Thus, he urged that statements be included that clearly define the agreement between the agencies. Dr. Hafs said Dr. Korwek had a point and that, as in the earlier case of EPA, these issues could be troublesome. Dr. Tolin said NIH is reviewing the scope of the NIH Guidelines and that ABRAC must take care to resolve the question of jurisdiction adequately and be consistent with NIH's actions.

Scope of Oversight

Dr. Tolin reminded the Working Group of its assignment to work on the exclusions for the scope of oversight. She said that she and Dr. Vidaver would work on exclusion (3), which deals with microorganisms.

The meeting was recessed at 5:30 p.m.

February 28, 1990

The meeting was called to order by Dr. Tolin at approximately 9:20 a.m. Dr. Tolin first reopened the discussion of confinement.

Confinement

Dr. Tolin distributed a draft table she had prepared which presents material on creating confinement levels by increasing stringency in scale, extent of measures to limit dispersal, extent of monitoring, and types of mitigation measures. (See Appendix C). She suggested specific reference to monitoring either as in this table or some other modification be added after Section IX-B-5.

Dr. Kemp said monitoring should vary according to the organisms involved. For example, for plants the confinement issue is movement of pollen beyond the plot. He suggested "time and space" be substituted for "inside/outside" which only considered distance, but not other aspects of monitoring. He said what goes on inside the plot may not be important from the biosafety point of view.

Ms. Cordle asked the Working Group to consider the basic question of what ought to be mentioned in the confinement section.

Dr. Tolin pointed out that the confinement section talks about principles, but doesn't describe practices. She said she believes the section would be better accepted if practices were described.

Ms. Cordle said there are two separate issues. One is inclusion of things which are not really confinement, per se, such as security and emergency response. The other issue is to develop examples of practices.

Dr. Tolin said there could be a separate section of issues which go across all confinement levels such as security, emergency response, maintenance, training, and termination of the experiment. The principles for these could be added before IX-C.

Dr. Payne said these practices would vary from experiment to experiment. For example, security could be very important or unnecessary. He said that termination of the experiment is extremely important. Dr. Vidaver agreed, saying that disposal should also be covered.

Dr. John Gerber, OAB, said he was confused because level (1) doesn't have any special procedures, yet level (1) organisms may spread beyond the plot. Dr. Tolin said that spread alone does not always cause a problem.

Dr. Vidaver suggested scale could be enlarged from what it is in the Table at level (1). She said one acre at level (1) would be very limiting. Dr. Tolin pointed out that some experiments would initially be conducted at higher confinement levels and then later redone at lower levels. Dr. Vidaver added that even at level (1) there should be some type of monitoring.

Dr. Hafs suggested the OAB staff draft a section which would cover such issues as monitoring, security, etc. Ms. Cordle said OAB would do so.

Dr. Kemp said the underlying philosophy of the ABRAC is to initially err on the side of caution and then gradually reduce the levels as experience is gained. He said this philosophy should be made clear to the IBCs.

Dr. Vidaver asked if the biosafety data generated from field tests would be collected and fed back into ABRAC and IBC deliberations. Dr. Tolin said that this is the role of NBIAP, which would then make the information available to ABRAC to aid in future decisions.

Ms. Cordle asked the Working Group to consider if, in the first publication of the USDA Guidelines, ABRAC should specify confinement levels, or should the Guidelines contain only principles. She said a lot of reviewers believe it would be less difficult to include only principles, at least initially.

Dr. Whitmore said the ABRAC discussed this at its last meeting and decided to stick with five confinement levels. Dr. Tolin said Dr. Fred Gould had advised ABRAC to eliminate the levels. Ms. Steinbock said ABRAC members had expressed widely varying opinions on this point at the last meeting. She said Dr. Gould had suggested delinking confinement level from level of oversight.

Dr. Whitmore said his impression was that the opposition to levels of confinement was from outside agencies. Dr. Payne said APHIS had argued against a formula with levels because absolute levels make it difficult to produce the documentation required by NEPA. He added that if an expert panel reviewed each confinement level arrived at by the PI, some of the problems with NEPA could be overcome.

Dr. Kemp asked if confinement levels are eliminated, isn't this a case-by-case review system? Dr. O'Berry said case-by-case is really no guidance at all. Dr. Tolin agreed, but added the USDA Guidelines needed to provide more guidance on confinement than they currently contain. Dr. Payne said the only way to move away from case-by-case review is to provide guidance and at least some suggested structure based on examples. He said ABRAC should avoid the appearance of a straightforward formula.

Dr. Kemp said that the only way to avoid the formula approach is to begin with a number of examples and specify appropriate confinement practices. He suggested that the examples of classification of parental organisms listed in Table 1 could be expanded to specify confinement practices for each of the organisms for each of the three types of modifications. He said this approach would be time consuming.

Dr. Tolin said this approach would give generalized guidance by analyzing specific model cases. Dr. Payne said this would be a good approach because it would allow ABRAC to build on experience. Ms. Cordle said she wasn't sure this type of exercise would lead to principles.

Dr. Kemp then suggested that ABRAC take the pragmatic approach and go to the public with the USDA Guidelines as they now stand for comment. Dr. Hafs agreed.

Dr. Payne said it was important not to publish something with obvious holes, and where any scientist could think of an example which didn't fit. The Working Group discussed several types of experiments where the current confinement scheme might not work.

Dr. Whitmore said that the diversity in problems led him to the conclusion that it might be wise to expand Table 1 and the examples to include confinement practices.

Ms. Cordle asked if Table 1 could be expanded to include principles. The principles could deal with concepts, like control of different mechanisms of dispersal.

Dr. Vidaver said the NIH Guidelines use levels and this has never been a problem. Dr. Payne said that the environment, however, is not an issue in the NIH Guidelines.

Dr. O'Berry recalled that an earlier table had associated practices with levels.

Ms. Cordle pointed out that the Handbook, An Introduction to Field Testing, (henceforth referred to as the Handbook), contains material on confinement that could be used in the USDA Guidelines. Ms. Steinbock said NBIAP had already convened expert panels to develop confinement practices for groups of organisms.

Ms. Cordle asked the Working Group what they considered adequate security for each confinement level. Dr. Vidaver said it would vary widely.

Dr. Hafs said the USDA Guidelines should provide general guidance on confinement, but it is incumbent on the PI to be creative and make a case for what is appropriate. Dr. O'Berry agreed, stating that the IBC needed to use prudent judgment as well. He said the more inflexible the USDA Guidelines become, the more difficult they will be to modify later on.

The Working Group reached consensus that more textual information is necessary, and that the USDA Guidelines should stay with confinement levels. Ms. Cordle said OAB staff would attempt to redraft Section IX on confinement and would ask guidance from ABRAC members as needed.

Dr. Tolin said perhaps the section could reference the Handbook. Ms. Cordle said OAB might draw on the NBIAP database. Dr. Kemp suggested moving the confinement levels to Section X of the USDA Guidelines. Mr. Stern suggested that Section IX might be renamed "Confinement Principles and Safety Protocol."

The Working Group reached agreement to work on a few examples of confined organisms to support the OAB effort in redoing the confinement section.

Level of Oversight

Ms. Cordle asked the Working Group to consider if the level of oversight should be tied to confinement levels. The Working Group agreed to discuss this point later.

Submissions Under the USDA Guidelines

Dr. Tolin asked the Working Group to discuss Section XI, "Submissions Under the USDA Guidelines." (using Doc. No. 119, p. 35-37) and Mr. Stern's redraft (Appendix D). She then explained the steps laid out in this section. She reminded the Working Group that they had agreed to reverse the order of Sections X and XI, so that the Guidelines provide guidance on the preparation of a document before it is determined to whom the document will go. She also added that the Working Group had agreed to designate Step 5 as preparation of the submission document.

Level of Oversight

Dr. Tolin reopened discussion on whether the level of oversight should be tied to confinement level. She presented several alternative schema that were distributed at the January ABRAC meeting for consideration. (See Appendix I.) She said the full ABRAC had concluded that level of oversight remain tied to confinement level.

Ms. Cordle expressed her concerns that confinement levels are subjective and judgmental. She said it would be difficult to go through an EIS process if oversight is tied to confinement levels.

Dr. Payne said that Dr. Fred Gould had argued against having confinement levels drive the level of review. (This is shown as Alternative 3 in Appendix I.)

Dr. Tolin said the USDA Guidelines were designed to have review of subjective judgments on confinement. Dr. Payne suggested that IBCs might review all confinement decisions even though requiring only notification. Dr. Hafs said such a system would significantly increase the workload of IBC's. Also, PI's would have to wait for a response from the IBC before they began their work.

Dr. Tolin noted that under the NIH Guidelines, IBC's are supposed to review all notifications. Dr. Hafs said that after IBC's get to know a PI and his/her work, they do not scrutinize each submission carefully since they are familiar with the organisms and the work habits and ethics of the PI's.

Dr. Tolin said there is precedent in the NIH Guidelines to have containment level drive level of review. Ms. Cordle asked if this has undergone any change. Dr. Tolin replied it was built in from the beginning.

Dr. Tolin said one alternative is to keep confinement level linked with level of review, but to require IBC review of all experiments initially. Alternatively, the lowest level of confinement could be set higher and then only IBC notification would be required in some cases.

Ms. Steinbock said that from the point of view of economics, it was unwise to require a higher confinement level than necessary. Dr. Vidaver agreed, saying that this was also the case from the scientific point of view. Dr. Payne said the whole point is to encourage people to select the appropriate confinement.

Dr. Kemp said there are experiments which shouldn't require IBC review, only notification.

Dr. Hafs said he liked alternative five which used confinement and other considerations to determine review level. He said he preferred flexibility, but, public opinion required a central point to catalog field releases, at least at present.

Ms. Cordle said she believed IBC notification is adequate for level (1) modified organisms. She said, however, that notification should be done in advance, so that if a mistake had been made by the PI, it would be caught by the IBC.

Dr. Tolin and Dr. Kemp disagreed, saying that this approach is not consistent with the way most IBC's are currently operating. Dr. Metzger said the IBC at his university often reviews notifications, in an expedited fashion at least by the Chairperson.

Dr. Whitmore said he found himself changing his mind and going back to Dr. Gould's position that confinement be delinked from the level of review, as displayed in Alternative 3.

Dr. Kemp asked how safety concern level (3) modified organisms would be dealt with in such a system.

Dr. Tolin suggested that for category (1) organisms IBC approval be required across the board. For category (2) organisms, IBC approval and USDA notification be required across the board. Dr. Vidaver agreed.

Ms. Cordle asked why USDA notification should be required. Dr. Tolin said this would be to begin to generate a database. Also, if OAB sees anything unusual they can inquire about it.

Dr. Tolin suggested that category (3) require USDA approval and ABRAC review across the board.

Ms. Steinbock and Ms. Cordle noted that the approach suggested by Dr. Tolin and generally favored by the Working Group was a reworking of Dr. Gould's suggestion, but with the boxes remaining displayed on the chart to give the appearance of having the flexibility for change in the future.

Scope of Oversight (review of assignments)

Drs. Kemp and Whitmore presented a reworking of exclusion (1) (Appendix D). He said that the scope had been split into three parts: macroorganisms/plants; macroorganisms/animals; and microorganisms.

Dr. Kemp then described how his redraft differed from (1) in Appendix A, p. 4. He noted that he had added a sentence which states that "the kingdom plantae includes the macro plants called brassicas as well as vascular plants." He said a definition of bryophytes could also be added.

Dr. Tolin asked if tissue culture is considered a traditional technique. She suggested an extra sentence be added to exclude tissue culture and vegetative propagation. She also asked if somaclonal variation is excluded. Dr. Kemp said it is excluded. Ms. Cordle suggested that the paragraphs be reordered to make this clear.

Dr. Tolin asked if certain algae and fungi are covered in exclusion (1). Dr. Kemp replied no, because they are not in the kingdom plantae.

Dr. O'Berry asked if there are any hazards associated with intrageneric embryo rescue. Ms. Cordle noted that Dr. Lois Miller had been opposed to excepting intrageneric embryo rescue at the last ABRAC meeting. Dr. Kemp said this concern had been addressed in his redraft.

Dr. O'Berry noted that Dr. Kemp's rewritten version is consistent with exclusion (2) for animals.

Dr. Hafs distributed the rewritten exclusion (2) for animals that he and Dr. O'Berry drafted (Appendix E). He said that they had decided to exclude vertebrates and arthropods, and not annelids and mollusks, because not enough was known about the latter organisms.

Dr. Kemp said that he believes enough is known about the processes to exempt all animals in exclusion (2).

Dr. Vidaver reaffirmed her view that only macroorganisms should be covered in exclusion (1) and exclusion (2). She distributed her rewrite of a definition for microorganism (Section III-A-4) and a rationale of exclusion (3) for microorganisms (Appendix F) which is based on a pragmatic definition of microorganisms, as organisms which are not visible to the human eye. Dr. Vidaver supported this approach saying that the public is mainly concerned about what they can't see. Dr. Tolin pointed out that such a definition is not biologically based, but that as long as this is explained it might be acceptable.

Dr. Kemp said this type of pragmatic definition would need to be discussed in the preamble.

Dr. Payne said such a definition would constitute a slight broadening of the BSCC option 4 scope.

Overview and Classification of the Parental Organism

Dr. Tolin handed out her redraft of Sections V and VI. She explained the changes she had made on the actions listed in these sections based on discussions by the Working Group. Dr. Kemp said that at first glance it was very clear. Ms. Cordle asked the Working Group to send OAB their comments on the redraft. (See Appendix G.)

Other Issues

Ms. Cordle noted that the Working Group had not had time to discuss the conflict of interest issue, specifically Sections II-B-4, "Direct Financial Interest" and II-B-5, "Engaged in Research." She said she had tried to find a solution through research on how other agencies were dealing with conflict of interest, but hadn't found anything applicable.

Dr. Tolin said that in practice the system is based on scientific integrity, but that this is difficult to document and explain to non-scientists.

Ms. Cordle said most codes of ethics are based around financial disclosure which is inappropriate for these Guidelines. She asked if ABRAC might consider using the NIH statement which is very short. She added that the public feels very strongly about this issue.

Dr. Metzger objected to the statement in the USDA Guidelines which states that it is the responsibility of the PI to know and obey all pertinent laws and regulations. He

suggested that this is an inappropriate directive. Dr. Metzger said the responsibility on compliance should rest on the institution, not the individual scientist.

Dr. Tolin said that this sentence needed to be in the USDA Guidelines to reinforce the concept that they did not supplant other regulations.

Mr. Stern said the individual scientist is legally responsible under the Plant Pest Act. Ms. Cordle agreed.

Ms. Cordle said the Handbook would help PI's become knowledgeable about what regulations apply. Dr. Metzger said he would look forward to seeing the Handbook.

Dr. Tolin adjourned the meeting at approximately 1:00 p.m.

MARTHA STEINBOCK
Rapporteur

ALVIN L. YOUNG
Executive Secretary

SUE TOLIN
Chairperson

DEPARTMENT OF AGRICULTURE
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20250

February 16, 1990

TO : MEMBERS OF THE ABRAC GUIDELINES WORKING GROUP

SUBJECT: SCOPE ISSUES

On February 27, 1990, the ABRAC Working Group will need to make recommendations on two scope issues for the Guidelines: (1) scope of organisms, and (2) the boundary between when the NIH Guidelines apply and when the USDA guidelines apply. To assist you in deliberations on these issues, I am enclosing the following:

1. A discussion paper on the scope of organisms definition with some suggested supporting information that might be used in the preamble of the Guidelines Notice when it is published for public comment, and

2. A discussion paper on the NIH -- USDA Guidelines boundary question.

The Biotechnology Science Coordinating Committee continues to work on the definition of organisms to be subject to oversight before their planned introduction into the environment, as was explained by Assistant Secretary Hess at the ABRAC meeting on January 5, 1990. However, at this time no decisions have been reached on the definition to be published by the Office of Science and Technology Policy in the FEDERAL REGISTER for public comment.

I look forward to productive discussions on the scope issues, and hope that the material provided will be helpful to you in preparation for the meeting.

Sincerely,

Maryln Cordle

Maryln Cordle
Senior Regulatory Specialist
Office of Agricultural Biotechnology

DEFINITION FOR "SCOPE OF ORGANISMS"

Statement of "scope" is one of the most critical parts of any proposed Federal action, and must be as clear and unambiguous as possible. Persons to whom the guidelines apply must be able to readily make that determination. Because compliance with the Guidelines will be mandatory for institutions receiving USDA funding, problematic legal issues of applicability may be arise unless the scope definition is clear.

At the last ABRAC meeting there was general support for a scope definition that used, as a starting point, deliberate genetic modification, and then defined specific additional exclusions.

Two definitions, using deliberate genetic modification as the starting point, have been proposed: (1) current ABRAC draft guidelines and (2) BSCC draft, which appears to have support from the majority of BSCC members.

<u>ABRAC draft</u>

> "...genetically modified organisms that result from deliberate insertion, deletion, or other manipulation of DNA or RNA".

"Organisms deliberately modified by the introduction of genetic material into, or manipulation of genetic material within, their genomes.[1]"

The basic difference between these two definitions is that the ABRAC definition specifically includes deletions of genetic material. It would be helpful for ABRAC to advise whether deletions should be included and the reason.

Both definitions include organisms whose genetic make-up has intentionally been modified by human intervention, and are not intended to cover organisms that result from natural reproduction or organisms which have only been "selected". Selection is the isolation of a desired organism from natural sources.

Both definitions identify a very broad group of organisms. The inclusion of an organism within the scope does not imply that it is dangerous or that it has any additional intrinsic risk as compared with naturally occurring organisms. The scope definition is intended to set the boundary around all organisms for which questions might be raised about whether new or unfamiliar safety assessment issues exist.

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[1] The term, "organisms" is intended to be inclusive and encompass the organisms of all kingdoms, including viruses. The term, "genomes" refers to the sum total of chromosomal and extrachromosomal genetic material of an organism. This would include the DNA and RNA of the chromosome, DNA or RNA in organelles, and DNA and RNA in the cytoplasm of an organism.

Exclusions

Within the scope definition, there is general agreement that specific exclusions should be provided. For discussion purposes I have suggested specific exclusion statements, followed by explanatory material, and then points for discussion. The exlusions are taxonomically arranged for convenience of discussion, as suggested at the last ABRAC meeting.

1. "Vascular plants that result solely from hand pollination, mutagenesis, or are regenerated from tissue culture, including those produced through selection of somaclonal variants, embryo rescue, protoplast fusion, or treatments that cause changes in chromosome number."

Vascular plants encompass those plants which contain small vessels that conduct fluid throughout the plant. Vascular plants are higher plants marked by the differentiation of tissues into organs such as roots, stems, leaves, and flowers. Crop plants, trees, and bushes are all vascular plants.

Many of the plants which are now major food crops were originally wild. Humans noted certain desireable qualities in these plants and began to aid the plant to propagate, for example, by hand pollination. Over the millennia, humans have selected plant species with desirable traits, taking advantage of the natural variation in plants. Through thousands of year, these practices termed "traditional breeding techniques", have

led to crop plants that are "domesticated" and may be very different from their wild ancestors.

Domesticated crop plants generally will not survive without human intervention. These crop plants have been selected by humans to possess certain desirable characteristics (e.g., larger grain heads, easier harvesting). Frequently, qualities which a breeder prizes are not those which would ensure survival in the wild. Humans, therefore, have provided "managed-ecosystems" with attendant conditions (e.g., irrigation, protection from insects, propagation measures) that are favorable to the plant's survival. The ability of these types of plants to survive without human intervention in natural environments is often limited.

Depending on the crop species, practices to confine the experimental crosses have been developed, and there is greater certainty about the efficacy of practices that are routinely followed to confine plants in an experimental field situation. Such practices have proved effective over the decades of crop breeding. Familiarity with the plants' life cycle, system of reproduction, and growth requirements has allowed for greater certainty about the probable behavior of the organism in the environment. Moreover, this familiarity leads to a knowledge of the range of potential phenotypic expression of the species in the environment.

Plants modified by traditional techniques such as mutagenesis and hand pollination are judged safe for field testing based on experience with hundreds of millions of crosses

that have been field tested. Current oversight mechanisms are adequate to address any risks that might be posed by their planned introduction into the environment.

As plant science advanced tissue culture became an important, efficient way of propagating plants. Tissue culture involves growing plant cells in a culture or medium that will support them and keep them viable. The culture can be started with plant organs (e.g., leaves or roots), tissues (e.g., epidermal cells of a leaf), and with single cells. In culture, isolated plant cells can be induced to undergo repeated cell division and growth. If culture conditions are adjusted, the cells will differentiate and grow into a plant. Tissue culture, then, is a process in which plant tissue is isolated from an adult plant and placed in a special media for the purpose of regenerating an adult plant without having to go through a normal reproductive cycle. Plants produced via tissue culture are genetically identical to the parent from which the specialized growth tissue was isolated.

Embryo rescue is a process wherein embryos that would otherwise probably die are treated to special culture conditions to increase their likelihood of survival. Generally, the type of embryo that would not survive is that which exhibits a basic incompatibility between the embryo and the maternal plant. Such a situation might arise, for example, when plants from different genera are crossed.

In protoplast fusion, cells are treated to remove their rigid outer walls and placed in conditions which permit the combining or melding (fusion) of two individual cells (sometimes from different species) into one cell. The fusion cell is then used to produce an adult, hybrid plant, via tissue culture. Thus, the restrictions imposed by natural breeding barriers can be circumvented, and the resulting plant would contain genetic material from both progenitor plant cells. There are still many limitations on the types of plants which can be produced through protoplast fusion, mainly due to the instability of chromosome pairing. Usually, most of the genetic information in the regenerated plant is from one of the parental cells.

Variants can be produced from a single parental plant when somatic cells of that plant are treated so that they form protoplasts and then plants are subsequently regenerated from those protoplasts. These variants are called "somaclonal variants." They are thought to result from mutations, deletions or rearrangements of the parental genetic material. Somaclonal variation can be used to generate plants from somatic tissue of the parent, thus by-passing the sexual process.

Vascular plants developed through regeneration in tissue culture are excluded because there is a long history of familiarity and safety with introductions of vascular plants *per se*. There is also a considerable body of experience that demonstrates safety and familiarity with the behavior of vascular plants treated with these techniques and regenerated through

tissue culture techniques. For several decades, plant varieties have been developed through these techniques which generally supplement traditional breeding techniques. Existing oversight mechanisms are adequate to address any risks that might be posed by the planned introduction of such plants developed through the use of these techniques.

The exclusion does not include nonvascular plants. These plants generally lack the extensive history of safety and familiarity that is available for vascular plants. Furthermore, adequate containment for some non-vascular plants may be problematic (e.g., with certain marine alae); and non-vascular plants often are found in non-managed, fragile, or threatened ecosystems.

Discussion points

1. Justification centers on domesticated vascular plants. Should the qualifier, domesticated, be added?
2. Are the excluded groups appropriate and adequately supported?
3. Are there any additional plant groups resulting from either traditional breeding or newer techniques that should be excluded? What is the supporting rationale?
4. Should the exclusion related to traditional breeding be separate from the exclusion related to regeneration from tissue culture.

2. "Vertebrate animals that result solely from artificial insemination, superovulation, or transfer of embryos."

Vertebrate animals refers to those animals with a backbone. The term vertebrate is used to identify those animals specifically, since the animal kingdom encompasses many life forms that may not readily come to mind as animals, such as insects, worms, or mollusks. Humans have selected vertebrate animals through "traditional breeding techniques." These breeding techniques allow humans to enhance characteristics they find desirable, (e.g., docility, ratio of body fat, feed efficiency). Such modifications of vertebrate animals have been conducted for centuries. Those qualities humans find desirable are generally not those which ensure survival of an animal in the wild. The domestication of animals has generally made them less able to survive in the natural ecosystem and more dependant on human intervention for survival. These animals are, therefore, bred and raised in management environments such as barns or open range.

Animal breeding has become more sophisticated through use of modern medical techniques such as artificial insemination, superovulation, and embryo transfer. These techniques are employed to increase the frequency of desired traits in a domesticated animal population. These breeding techniques are generally applied only to animals being raised in a setting where

the population is routinely confined and managed to ensure survival. Familiarity with the animal's life cycle, system of reproduction, and range of phenotypic expression in the environment allows us to predict probable behavior. In general, existing oversight mechanisms address any risks that might be associated with planned introduction into the environment of domesticated animals.

Discussion points

1. Justification centers on domesticated vertebrate animals. Should the qualifier, domesticated, be added? Consider fish and other wild life breeding in this context.

2. Is the exclusion appropriate; should it be extended further? What supporting rationale is appropriate?

3. Microorganisms modified solely: (a) through chemical or physical mutagenesis; (b) by the movement of nucleic acids using physiological processes including, but not limited to transduction, transformation, or conjugation: or (c) by plasmid loss or spontaneous deletion. If nucleic acid molecules produced using in vitro manipulation[2] are transferred using any of the

[2] In vitro manipulation includes: the directed addition to, rearrangement of, or removal of nucleotide sequences from the genetic material that is introduced; or, the use of chemical or physical techniques to enrich for a specific sequence.

techniques listed in (a) through (c), the resulting organisms do not fall under this exclusion.modifications to nucleic acids

This exclusion applies to a class of organisms, microorganisms, which differ in several respects from the organisms described in the first two exclusions. First the term "microorganism" covers a wide range of types of organism; viruses, bacteria, fungi, algae, etc. The life cycles, reproductive behaviors and adaptive strategies of these different types of microorganism can vary enormously.

The most important difference between microorganisms and other organisms for the purposes of this discussion is that while some classes of microorganism do not possess an ability to exchange genetic material through the types of sexual processes associated with plants and animals, they do possess various mechanisms to exchange genetic material in pseudosexual ways.[3]

Microorganisms engage in such exchanges through: (1) transduction, a process in which a virus can pick up nucleic acid from one host and transfer it to a subsequent host; (2) transformation, a process in which the microorganism takes up DNA from the environment (perhaps released into the environment by the death of another microorganism) and incorporates the DNA into its genome; and (3) conjugation, a process in which genetic

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[3] Some classes of microorganisms possess mechanisms for asexual propagation, such as binary fission, budding, and asexual spore formation. The proposed definition is not intended to cover organisms that result from asexual reproduction.

material is transferred from one microorganism to another through physical contact.

We are familiar with these processes and know that they occur in nature. One can argue, therefore, that when a microorganism is modified by recreating in the laboratory conditions under which these types of genetic exchanges can occur, it is likely that the resulting organism is a variant that exists in nature. The conditions for exchange may have been optimized in the laboratory for efficiency, but the exchange is not qualitatively different.

Microorganisms, as are other organisms, are often exposed in the natural environment to chemical substances called mutagens, or physical agents such as ultraviolet light or x-rays which cause modification in genetic material. Treatment of organisms with chemical or physical mutagens in the laboratory only accelerates natural phenomena. Here again one can argue that when an organism is modified by recreating in the laboratory conditions which occur in nature, the result will likely be organisms not significantly different from those found in nature.

Another means by which genetic changes take place in nature is through loss of genetic material. Genetic material can be spontaneously deleted from chromosomal and extrachromosomal elements. In some cases, large segments of genetic material, e.g., plasmids, may be lost. Similar types of changes brought about in the laboratory would result in organisms that are variants likely to exist in nature.

This is not to say that because an organism occurs in nature it is safe. Rather, if the organism occurs naturally in the environment we are more likely to have observed its interaction with the environment, and better understand the risks that it might pose. It is also more likely that existing oversight mechanisms are adequate to address any risks that might be posed by these organisms.

Microorganisms modified by the introduction of *in vitro* manipulated nucleic acids are not covered by this exclusion. *In vitro* modifications to nucleic acids include *in vitro* treatment with enzymes and *in vitro* joining of nucleic acid sequences. They would also include the application of chemical or physical techniques to enrich for particular nucleic acid sequences, for example, use of the polymerase chain reaction, and the use of sequence-specific DNA affinity columns. These are powerful techniques that can be used to change organisms sufficiently that we might not be familiar with the resulting phenotype and their potential range of interactions in nature.

Discussion points

1. Is the exclusion appropriate?
2. Is the explanation adequate?

4. Organisms which have been modified by the introduction of non-coding, non-expressed nucleotide sequences that cause no phenotypic or physiological changes in the parent organism,

provided that a notification of the claimed exemption was provided to an institutional biosafety committee (described in Section XII-B) at least 30 calendar days before the research begins, and no written notice from the institutional biosafety committee objecting to the claimed exemption, was received within 30 days of the notification.

This exclusion applies to organisms that have been modified by the introduction of *in vitro* manipulated nucleotide sequences that serve only to identify the organism's genome. The exclusion also includes organisms that have been modified by the addition of short nucleotide sequences whose sole function is to facilitate subsequent *in vitro* genetic manipulation, or so-called "linker" sequences. To qualify for this exclusion, it should be demonstrated that the inserted nucleotide sequences are non-coding and non-expressing and no change in phenotype will occur due to the insertion.

These non-coding, non-expressing sequences should be well-characterized, including knowledge of the nucleotide sequence, of the site of insertion, and the effects of inserting material in that site. The exclusion does not apply to organisms modified by the introduction or manipulation of non-coding nucleotide sequences that function in gene regulation.

When these conditions are met, no "new" or unfamiliar safety assessment issues pertaining to introduction into the environment

of these organisms would exist compared to the parental organisms that have not been modified in this manner.

Discussion points

1. Is the exclusion appropriate; is an IBC notification of claimed exemption the best way to handle this type of exclusion? BSCC likely will recommend an exclusion for non-coding, non-expressing sequences, leaving the mechanism for implementation to the agencies.

5. Organisms other than those exempted in 1-4 above, if it can be demonstrated that: (1) they could be readily produced by the techniques listed above; and (2) there is sufficient familiarity with the organism to foresee environmental effects equivalent to those associated with past safe introduction of similar organisms in similar target/test environments. Such claims with supporting information may be submitted to the Office of Agricultural Biotechnology for review by ABRAC and a decision by the Assistant Secretary for Science and Education. A section of the Guidelines is reserved for listing all organisms that USDA finds on review to qualify under this exemption.

This exclusion recognizes that a specific genetic modification can be made in a specific organism by a number of different techniques. What is important in assessing the resulting organism is not the method by which the modification was made, but the phenotype resulting from that specific

modification. For example, chemical and physical mutagenesis techniques can be used to modify an organism. Selective techniques can then be used to isolate from among its descendants, organisms modified in a particular phenotypic trait. An organism modified in that same phenotypic trait can, however, also be made by use of other genetic modification techniques, including procedures such as recombinant DNA.

The first four exclusions describe both categories of organisms and techniques of genetic modification. This approach is employed because: (1) for the most part the categories named in the exclusion consist of organisms with which we are familiar; and (2) information on the process by which a specific organism is modified can be valuable in predicting the probable characteristics of the organism and its potential effect on human health and the environment. When we know, for example, that plant is to be modified by a traditional breeding techniques, we have sufficient familiarity with the parental plants, including their range of potential phenotypic expression, to predict probable behavior of the hybrid off-spring in the environment.

While the proposed exclusions include elements of technique, the scope definition with its exclusion is not a process based definition. The fifth exclusion removes from the scope, organisms that fall into the categories of excluded organisms listed in exclusion one through three, but are generated through techniques other than those listed in exclusion one through three, if two conditions are met.

First, they could be readily produced by the techniques listed in exclusion one through three. Second, there is sufficient familiarity with the organism and their descendants to foresee environmental effects comparable to past safe introductions of similar organisms in similar target/test environment.

When these requirements are met the resulting modified organism should possess a phenotype which falls within the range of phenotypic expression of the species. No new or additional assessment issues would be raised when such an organism is introduced to the environment, and existing oversight mechanisms should be adequate.

A mechanism is provided for USDA to make exclusionary determinations on request for specific organisms meeting the criteria, and to maintain a listing of such determinations and provide public notification in the FEDERAL REGISTER.

Discussion points

1. Is this exclusion workable and desireable?

2. Are there any other exclusions that should be considered?

JURISDICTION RE: NIH AND USDA GUIDELINES

We need to carefully examine the boundaries for the USDA Guidelines to clarify when the USDA Guidelines will apply and when the NIH Guidelines will apply.

It is proposed that:

a. the USDA Guidelines apply when agricultural research is conducted outdoors, i.e., not conducted within an enclosed structure with walls, roof and floor, such as a laboratory or greenhouse. (Note that agricultural research has not been defined.[4])

b. the NIH Guidelines apply to agricultural research involving recombinant DNA organisms when that research is conducted within an enclosed structure.

Discussion. NIH soon will adopt Appendix Q, which provides for outdoor testing of animals at containment level, BL-1. This will create an overlap with the USDA Guidelines. Once the USDA Guidelines are adopted, IBC's need to understand that agricultural research, that otherwise would fall under Appendix Q, BL-1, should be reviewed under the USDA Guidelines.

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[4] Whenever USDA funding is involved, USDA has jurisdiction. Defining "agricultural research" would be important when federal funding is not involved, and there is a need to know which set of guidelines are appropriate for voluntary compliance.

Who should review agricultural research to be conducted within an enclosed structure, when the containment proposed is less than required by the NIH Guidelines? NIH or USDA?

If the decision is USDA, then the following definition proposed for a contained facility in the January 10, 1990 draft of the USDA Guidelines, is appropriate.

> "Contained facility" refers to an enclosed structure with walls, roof, and floor (e.g., a laboratory or greenhouse) that also meets the provision of the NIH Guidelines (emphasis added).

If the decision is NIH, then the underlined part of the definition needs to be deleted. Also, a footnote should be added to the definition to read, "Research involving recombinant DNA molecules conducted in a contained facility, should meet the containment conditions provided in the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules.

Should we add "barn", to the examples of an enclosed structure?

Who should review research proposed for livestock housed in a barn, with no outdoor component?

It is anticipated that several years may pass before USDA has published an Environmental Impact Statement for the Guidelines, formally adopted the Guidelines, and amended its regulations which now require that research funded by USDA be conducted in compliance with the NIH Guidelines. To provide for an appropriate transition during this time period when case-by-case reviews will be conducted by USDA, we have worked out a process with NIH. NIH will review the "USDA (Science and Education) approval process" (as was done with the APHIS process) looking at the record from several reviews. When they are satisfied that the process is equivalent to the NIH process, future reviews and approvals will automatically be accepted in lieu of NIH approval.

Long term, we will want to consider whether USDA should take over responsibility for those parts of the NIH Guidelines pertaining to agricultural research conducted in containment, in particular Appendices P and Q which NIH soon plans to publish. However, short term the issue can be viewed more narrowly.

Table 10–2 *Classification of Living Organisms Traditionally Regarded as Plants. (See Appendix C for summary descriptions of these groups.)*

Prokaryotes		
Kingdom Monera	Bacteria	
Eukaryotes		
Kingdom Protista	Heterotrophic protists	Division Oomycota (water molds) Division Chytridiomycota (chytrids) Division Acrasiomycota (cellular slime molds) Division Myxomycota (plasmodial slime molds)
	Photosynthetic protists ("algae")	Division Chrysophyta (diatoms and chrysophytes) Division Pyrrophyta (dinoflagellates) Division Euglenophyta (euglenoids) Division Rhodophyta (red algae) Division Phaeophyta (brown algae) Division Chlorophyta (green algae)
Kingdom Fungi	Fungi	Division Zygomycota (zygomycetes) Division Ascomycota (ascomycetes) Division Basidiomycota (basidiomycetes)
Kingdom Plantae	Bryophytes	Division Bryophyta (bryophytes) Class Hepaticae (liverworts) Class Anthocerotae (hornworts) Class Musci (mosses)
	Vascular plants Seedless vascular plants	Division Psilophyta (psilopsids) Division Lycophyta (lycopods) Division Sphenophyta (horsetails) Division Pterophyta (ferns)
	Seed plants	Division Cycadophyta (cycads) Division Ginkgophyta (ginkgo) Division Coniferophyta (conifers) Division Gnetophyta (gnetophytes) Division Anthophyta (angiosperms) Class Dicotyledones (dicots) Class Monocotyledones (monocots)

cluded in this book are discussed in Chapter 14, and the three major groups of algae—green algae, brown algae, and red algae—in Chapter 15. Discussions of the heterotrophic protists known as protozoa—in other words, those that have historically been treated as animals instead of as fungi—are not included in this text.

In summary, the kingdom Protista includes a very heterogeneous assemblage of unicellular, colonial, and multicellular eukaryotes that do not have the distinctive characteristics of the animals, plants, or fungi.

Kingdom Animalia

The animals are multicellular organisms with wall-less eukaryotic cells lacking plastids and photosynthetic pigments. Nutrition is primarily ingestive with digestion in an internal cavity, but some forms are absorptive, and a number of groups lack an internal digestive cavity. The level of organization and tissue differentiation in complex animals far exceeds that of the other kingdoms, particularly with the evolution of complex sensory and neuromotor systems. The motility of the organism (or, in sessile forms, of its parts) is based on contractile fibrils. Reproduction is predominantly sexual. Animals are not discussed in this book, except in relation to some of their interactions with plants and the other organisms that are treated here.

Kingdom Fungi

Fungi (see Figure 10–6) are nonmotile filamentous eukaryotes that lack plastids and photosynthetic pigments and absorb their nutrients from either dead or living organisms. The fungi have traditionally been grouped with plants, but there is no longer any doubt that the fungi are in fact an independent evolutionary line

KINGDOM PLANTAE

The plants are autotrophic (some are derived heterotrophs), multicellular organisms possessing advanced tissue differentiation. All plants have an alternation of generations, in which the diploid phase (sporophyte) includes an embryo, and the haploid phase (gametophyte) produces gametes by mitosis. Their photosynthetic pigments and food reserves are similar to those of the green algae. Plants are primarily terrestrial.

DIVISION

DIVISION BRYOPHYTA: Liverworts, hornworts, and mosses. The bryophytes have multicellular gametangia with a sterile jacket layer; their sperm are biflagellated. The gametophytes and sporophytes of bryophytes both exhibit complex multicellular patterns of development; conducting tissues, which are not as specialized as the xylem and phloem of vascular plants, are present only in mosses. Most photosynthesis in these primarily terrestrial plants is carried out by the gametophyte, upon which the sporophyte is dependent, at least initially. There are about 16,000 species.

Class Hepaticae. The liverworts. The gametophytes are thallose or leafy, the rhizoids are single-celled, and the sporophytes, which lack stomata, are relatively simple structures. There are about 6000 species.

Class Anthocerotae. The hornworts. The gametophytes are thallose. The sporophyte grows from a basal intercalary meristem for as long as conditions are favorable. Stomata are present on the sporophyte. There are about 100 species.

Class Musci. The mosses. The gametophytes are leafy. Sporophytes have complex patterns of dehiscence. Rhizoids are multicellular. Stomata are present on the sporophyte. There are about 9500 species.

DIVISION PSILOPHYTA: Psilopsids. Homosporous vascular plants, one of which has leaflike appendages on the stem; both have extremely simple sporophytes, with no differentiation between root and shoot. Motile sperm. There are two genera and several species.

DIVISION LYCOPHYTA: The lycophytes. Homosporous and heterosporous vascular plants characterized by the presence of microphylls; the lycophytes are extremely diverse in appearance. All lycophytes have motile sperm. There are five genera, with about 1000 species.

DIVISION SPHENOPHYTA: The horsetails. A single genus of homosporous vascular plants, *Equisetum*, with jointed stems marked by conspicuous nodes and elevated siliceous ribs. Sporangia are borne in a strobilus at the apex of the stem. Leaves are scalelike. Sperm are motile. There are 15 living species of horsetails.

DIVISION PTEROPHYTA: The ferns. Mostly homosporous, although some are heterosporous. All possess a megaphyll. The gametophyte is more or less free-living and usually photosynthetic. Multicellular gametangia and free-swimming sperm are present. There are about 12,000 species.

DIVISION CONIFEROPHYTA: The conifers. Gymnosperms with active cambial growth and simple leaves; ovules and seeds exposed; sperm nonflagellated. The most familiar group of gymnosperms. There are some 50 genera, with about 550 species.

DIVISION CYCADOPHYTA: The cycads. Gymnosperms with sluggish cambial growth and pinnately compound, palmlike or fernlike leaves; ovules and seeds exposed. The sperm are flagellated and motile but are carried to the vicinity of the ovule in a pollen tube. There are 10 genera, with about 100 species.

DIVISION GINKGOPHYTA: Ginkgo. Gymnosperm with considerable cambial growth and fan-shaped leaves with open dichotomous venation; ovules and seeds exposed; seed coats fleshy. Sperm are carried to the vicinity of the ovule in a pollen tube but are flagellated and motile. There is only one species.

DIVISION GNETOPHYTA: Gnetophytes. Gymnosperms with many angiospermlike features, such as vessels; the gnetophytes are the only gymnosperms in which vessels occur. Motile sperm are absent. There are 3 very distinctive genera, with about 70 species.

DIVISION ANTHOPHYTA: The flowering plants. Seed plants in which ovules are enclosed in a carpel and seeds are borne within fruits. The angiosperms are extremely diverse vegetatively but are characterized by the flower, which is basically insect-pollinated. Other modes of pollination, such as wind pollination, have been derived in a number of different lines. The gametophytes are much reduced, with the female gametophyte often consisting of only seven cells at maturity. Double fertilization involving the two sperm of the mature microgametophyte gives rise to the zygote (sperm and egg) and to the primary endosperm nucleus (sperm and polar nuclei); the former becomes the embryo and the latter becomes a special nutritive tissue, called the endosperm. There are about 235,000 species.

Class Monocotyledons. The monocots. Flower parts are usually in threes; leaf venation is usually parallel; primary vascular bundles in the stem are scattered; true secondary growth is not present; there is one cotyledon. There are about 65,000 species.

Class Dicotyledons. The dicots. Flower parts are usually in fours or fives; leaf venation is usually netlike; primary vascular bundles in the stem are in a ring; many with a vascular cambium and true secondary growth; there are two cotyledons. There are about 170,000 species.

Some other common terms used to describe major groups of plants deserve mention here. In systems in which the algae and fungi are regarded as plants, they are often grouped as a subkingdom, Thallophyta, the thallophytes: organisms with no highly differentiated tissues, such as root, stem, or leaf, and no vascular tissues (xylem and phloem). The bryophytes and vascular plants are then grouped into a second subkingdom, Embryophyta, in which the zygote develops into a multicellular embryo still encased in an archegonium or an embryo sac. All embryophytes are marked by an alternation of heteromorphic generations.

Although they are no longer used in formal schemes of classification, terms such as "algae," "thallophytes," "vascular plants," and "gymnosperms" are still sometimes useful in an informal sense. An even earlier scheme divided all plants into "phanerogams," for those with flowers, and "cryptogams," for those lacking flowers, these terms are occasionally seen today as well.

USE OF PRACTICES FOR CREATING CONFINEMENT LEVELS

PRACTICES	4	3	2	1
Scale--numbers of organisms released	**Lowest practicable number to allow** measurement of a specific risk parameter	Lowest practicable number to allow statistical measurement of performance		No limit, up to one acre, familiar
Extent of use of measures to limit dispersal and establishment, i.e., physical, biological, chemical, environmental	Extensive--best with at least two back-up measures	Best with one back-up	Best alone	None other than biological or environmental
Extent of monitoring, i.e., ease, accuracy, sensitivity	Frequent monitoring within and outside of experimental area and accessible environment	Frequent monitoring within, infrequent outside	Infrequent monitoring within, no monitoring outside	No monitoring
Extent of mitigation measures in terms of efficacy	All available measures applied within and outside experimental area--Best with a back-up	Applied only in the accessible environment--Best	Applied only within the experimental area--Most practical	None, except in emergency
		control	confine	familiar

Scope Exclusions: Plants

Plants that are produced by:

Selection and breeding using natural regeneration
Hand pollination
Physical or chemical mutagenesis
Organ, tissue, or cell culture
Selection and propagation of somaclonal variants
Chemical treatments that cause changes in chromosome number
Embryo rescue

Plants are those organisms in kingdom plantae as designated in Raven, Biology and Plants (Appendix B).

Scope Exclusions

2. Animals that result solely from breeding techniques such as natural selection, artificial insemination, superovulation, embryo transfer, and embryo splitting.

Animals refer to all macroorganisms which are members of the animal kingdom. Included are domesticated, vertebrate and arthropod species, as well as such diverse organisms as insects, fish, mollusks and other free-living creatures.

The principles of animal breeding have grown out of nearly three centuries of practical experience, perfected by the science of quantitative genetics over the last 50 years. Our greatest understanding is among cattle. In dairy cattle, for example, these proven genetic principles currently result in production efficiencies in the U.S. exceeding 150 lbs. of milk per cow. The same breeding principles have been applied to produce animals that are faster growing, leaner, more prolific and much more efficient. There is a growing body of evidence that the same genetic principles apply for less traditional animal species. For example, in fish (catfish), insects (drosophila) and nematodes (C. elegans) most of the genome has been mapped. In general, knowing the heritability of any multiple allelic trait, one may reliably predict the changes which will result from any given breeding plan, regardless of species.

Although the procedures of superovulation, embryo transfer and embryo splitting are relatively new, they are now widely used with no examples of adverse effects. They are natural extensions of traditional animal breeding principles.

Thus, there exists an extensive experiential base with these excluded methods broadly among animal species. Animal life cycles are sufficiently understood that one may reliably predict the genotypic and phenotypic outcomes of these kinds of research. Existing oversight mechanisms are adequate for the risks associated with planned introductions of animals into the environment resulting solely from these techniques.

SCOPE - MICROORGANISMS

For purposes of these guidelines, microorganisms are defined as those living organisms not visible to the human eye. This includes not only viruses, bacteria, and fungi, but also certain algae, insects and nematodes. This is an operational definition to encompass all reproducing entities with which the scientific community and public have expressed concerns.

The rationale for excluding microorganisms from oversight that are produced by conventional processes (3a, b, c) or other processes (4) is that (a) no fundamentally new scientific principles are expected to arise from those with which we are familiar and (b) no new biosafety issues are expected. This does not imply that either the organism or the conventionally modified organisms are safe, only that no new issues in the evaluation of their safety are expected.

The alternative to exemption is for yet another new tier or mechanism of oversight for microorganisms with which we are not familiar, which can be construed by many scientists as virtually all but a handful of microorganisms. With over 20,000 named species of bacteria and 40,000 of fungi alone, for example, should a mechanism be considered for each case? Who will oversee the research; what level of concern is there; e. g. of modifications by chemical or physical mutagenesis; do the costs outweigh the benefits and risks, etc. All the processes considered for exemption have either been well-studied or can be predicted to accelerate natural phenomena. From a purely logical standpoint, the "familiarity" concept can be questioned. Some in the scientific community would even question the well-known examples in the NRC report.

There is no perfect oversight answer because "a variety of competing considerations must be balanced (emphasis added); various viewpoints or perspectives cannot always be accommodated, or even reconciled" (Korwek, 1990). Based on the lack of evidence that the microbial exemptions present a probable unacceptable risk to humans or the environment, no additional oversight appears justified; speculative risks here appear even more problematic than with the newer biotechnological processes which are covered in the Scope.

Korwek, E. L. 1990. Releases of organisms into the environment: options to trigger, exempt products from oversight. Chemical Regulation Reporter. Feb. 16, 1990. pp. 1454 - 1458.

2/28/90 DRAFT REVISION - SATOLIN
ABRAC GUIDELINES WORKING GROUP

V. Overview: Guidelines for Safe Conduct of Research

The purpose of this section is to provide guidance to investigators for conducting research with a genetically modified organism outside of a contained facility. The conditions under which such research can be conducted safely should be assessed relative to the conditions that are normally accepted for conducting research with the parental organism.

~~Thus,~~ The evaluation of conditions for research with the genetically modified organism begins with an assessment by the principal investigator of the conditions for research with the unmodified, or parental, organism. Section VI sets out a framework for conducting this assessment, leading to determination of a level of safety concern for the parental organism in a specific environment.

After the level of safety concern for the parental organism has been determined, investigators are guided to consider the effect of the genetic modification. Section VII sets out a framework for assessing whether the modification affects the level of safety concern, and how as conclusion is reached that the modification has no affect on the level, or increases or decreases the level. A safety concern level is then assigned to the genetically modified organism, ~~as presented~~ in accordance with Section VIII. The process of making the modification is used in this assessment, since knowledge of the

precise modification may allow better predictability of the safety of the organism and its products, and thus allow approriate confinement and other safety practices for the research to be selected.

~~At this point,~~ Principal investigators should then select appropriate confinement and other biosafety conditions for the research. Section IX establishes confinement principles that can be applied to the design of appropriate levels of confinement for ~~the~~ experiments.

The above information is summarized in the form of a submission document, using the suggested format in Section X. This document is then used to obtain proper reviews and approvals as described in Section XI.

These actions are
~~This can be~~ summarized in the six steps below.

Step 1. Determine level of safety concern for parental organism for the specific accessible environment.

Step 2. Determine effect of the genetic modification on safety

Step 3. Determine level of safety concern for the modified organism

Step 4. Determine confinement level appropriate to the particular level of safety concern for the modified organism, and develop a safety protocol to meet this level of confinement.

Step 5. Prepare a summary with documentation for submission

Step 6. Obtain necessary review and approval.

VI. Step 1. Determination of the Level of Safety Concern for Parental Organisms

~~Parental Organisms~~

To determine the level of safety concern, the attributes of an organism can only be evaluated within the context of the environment in which the research is to be performed. Particular attributes of an organism should be identified and evaluated together with its ecological relationships with other organisms in the environment accessible to it in the absence of confinement. Principal investigators should be aware that the degree of detail and documentation for the evaluations made under this section will not be the same for all organisms. ~~In~~ Additionally, information on all attributes may not be available or appropriate for every organism. ~~However,~~ There may also be information relevant to safety that is not specifically mentioned in the Guidelines but that is ~~available~~ known for the organism. Principal investigators should utilize as much information as possible that is relevant to assessing the potential for adverse effects on human health or on managed or natural ecosystems of the particular organism.

~~VI~~-A. Organism Attributes

The attributes which should be considered for determining the level of safety concern for parental organisms in the accessible environment are:

- the pest/pathogen status and potential of the parental organism,
- the potential of the parental organisms to become established ~~itself~~ in the accessible environment,

- the ecological relationships of the parental organism with other organisms in the accessible environment,

- the potential of the parental organism for inducing genetic change in natural or managed populations in the accessible environment,

- the potential for monitoring and control of the parental organism.

VI-B. Classification Procedure

1. ACTION I. Determine the environment accessible to the organism.

This is to be interpreted as the area in and immediately surrounding the site of the research location into which the organism is to be introduced, and into which the organism could conceivably have access.

2. ACTION II. Determine the relevant attributes of the parental organism as they relate to the accessible environment.

This may be done by addressing the following questions or issues.

2a. Pest/pathogen status and potential.

(1) What are the plausible adverse effects of the organism on the accessible environment due to its being a pest or pathogen? These include, for example, lowered productivity of economically

important organisms, damage or destruction of natural habitats, and adverse effects on human health.

(2) Will the potential extent of the adverse effects be greater than already exists in the accessible environment because of this introduction?

(3) What is the potential for exchange of genetic information between the organism and pests or pathogens in the accessible environment? In other words, what is the likelihood ~~for~~ of the organism becoming a pest or pathogen through the exchange of genetic information under the conditions of the experiment?

(4) Does the organism have any ecological characteristics that might increase or decrease its pest/pathogen potential? For example, if the organism and its relatives are restricted to a narrow ecological neche, does this imply that the potential to broaden that niche and become a pest might be expected to be low?

2b. Potential for establishment in the accessible environment.

(1) What are the known mechanisms of survival or persistence of the organism in the natural environment? Are there natural predators or other organismal relationships that affect its survival? Are there climatic and edaphic or other abiotic factors influencing survival of the organism?

(2) What are the known mechanisms of dissemination for the organism?

(3) Is population size known to affect the ability of the organism to become established in an environment?

(4) What information is known about the competitiveness and aggressiveness of the organism in the accessible environment in relation to the ability of the organism to become established in that environment?

2c. Ecological relationships with other organisms in the accessible environment. The importance of the organism to the structure of the ecological community should be considered. The following items are suggested as a framework for this assessment.

(1) Is the organism known to be involved in any critical ecosystem function, e.g., nitrogen fixation, inorganic nutrient uptake? Is it a key food chain component or does it provide a critical habitat for a key species? Is involvement of the organism in critical ecosystem functions indirect or direct? Can other organisms in the ecosystem fulfill its function?

(2) Is the organism known to have any ecological specificity and range of interactions with other organisms?

(3) What is the geographic range of the organism? Is it small or large? Are there changes that ~~could~~ have occurred in it that have broadened or narrowed its geographic range?

(4) What is the habit or the organism? Is it free-living, mutualistic, pathogenic, parasitic, or symbiotic? Does its habit relate to any potential adverse effects on the environment should it escape from confinement? Will its habit facilitate monitoring and control?

2d. Potential for inducing genetic change in natural or managed

populations in the accessible environment.

An evaluation as to whether an organism might have attributes contributing to this ~~potential~~ assessment point may address the following ~~points~~ issues:

(1) Is there intrinsic genetic instability within the genome of the organism, such as the ability of the organism to incorporate exogenous DNA? Are active transposable elements present? Are active viral elements present that interact with the normal genome? Have any mutations been observed that result in an unusual genotype or phenotype?

(2) Is there a [redacted] natural or managed interbreeding population known? What is its size? What is the degree of genetic diversity in that population? Is there any potential for genetic exchange between the specific organism being introduced into an environment and any organisms in the natural population in that environment?

2e. Potential for monitoring and control.

(1) Is information from prior experiments, both contained and outside of containment, available that has demonstrated that the organism can be controlled by various means, such as those using biological, environmental, physical, or chemical approaches?

(2) What monitoring methods are available? Can they be performed routinely? What is their sensitivity and degree of accuracy? Are they reasonable in cost?

(3) Are there special procedures that could be applied to minimize any inadvertent release or escape of the [redacted] organism beyond the boundaries of the research site?

VI-A-2. ACTION III. Determine the relative importance of the

specific attributes in the context of the planned research. In order to do this, an analysis of the attributes is made, and those that appear to be most critical or influential in the ability of an organism to cause adverse effects are identified.

VI-A-3. ACTION IV. Choose a level of safety concern for the parent organism from among the five possible levels described below. The principal investigator, in the summary document, provides a rationale and justification for assigning this safety concern level for the organism in the environment of the test. The assignment should be based on the attributes described in Action II, and identified in Action III as important. It should be noted that the questions and issues raised above are not meant to be all inclusive.

The attributes identified below in the section describing safety concern levels are likewise not meant to be all inclusive. The possession of a single attribute listed under Level 1, for example, does not necessarily indicate that the organism should be assigned to Level 1. Furthermore, an organism does not have to possess all attributes to qualify for a Level 1 assignment. Level assignment requires scientific judgement and interpretation, as well as a justification for the action taken.

VI-A-1. Level 1. Organisms whose ecological attributes in the specified accessible environment are well understood, and to the extent that it can be determined, the organism has virtually no potential for adverse effects on human health or on managed or

natural ecosystems. Selected attributes that may indicate this lowest level of safety concern are:

a. no history of having caused adverse effects in the accessible or similar environments

b. the low evolutionary potential to become a harmful organism

c. the inability to survive in the accessible environment beyond the time necessary for the planned research.

d. the low probability of exchange of genetic information with native populations of organisms.

e. the fact that an organism is indigenous to the accessible environment.

f. the existence of practical techniques to minimize escape of viable organisms from the research site.

g. the existence of practical techniques to recapture or kill escaped organisms before any adverse effects occur.

2. Level 2. Organisms that may cause adverse effects on human health or on managed or natural ecosystems, the consequences of which are predictably low.

3. Level 3. Organisms that may cause adverse effects on human health or on managed or natural ecosystems, the consequences of which are predictably moderate.

4. Level 4. Organisms that may cause adverse effects on human health or on masnaged or natural ecosystems, the consequences of which are predictably high.

5. Level 5. Organisms that have ecological attributes in a specified accessible environment that indicate the organism may cause adverse effects on human health or on managed or natural ecosystems, the consequences of which are predictably high, and no feasible types of confinement will allow research to be conducted safely outside of contained facilities. Selected attributes that

may indicate this highest level of concern are:

a. a history of adverse effects caused by the organism in the accessible environment or in similar environments.

b. the ability of the organism to survive and proliferate in the accessible environment.

d. the fact that the organism is not indigenous to the accessible environment.

c. the tendency of the organism to have a high frequency of exchange of genetic information with native populations of organisms.

f. the lack of adequate techniques to recapture or kill escaped individuals before adverse effects occur.

e. the lack of effective techniques to minimize escape of viable organisms or active products from the research site.

TABLE 1.

EXAMPLES OF DETERMINING LEVEL OF SAFETY CONCERN
FOR UNMODIFIED ORGANISMS (1)

Organism	Pest/ pathogen status	Ability to establish	Ecological relationships	Potential for genetic change	Potential for monitoring & control	Overall level of concern
Zea mays (maize)	1 (2)	1	1	1	1	1
Bos taurus (cattle)	1	1	2	2	1	1
Butyrivibrio fibrisolvens (rumen bacterium)	1	1	1	1	1	1
Brassica napus (rapeseed) Southwest U.S.	1	2	1	2	1	1
Brassica napus (rapeseed) Pacific NW	3	3	3	4	1	3
Cardiochiles nigriceps (parasitic wasp)	1	4	1	1	3	1
Drosophila melanogaster (wild type lab strains)	1	2	1	1	3	2

(1) Information developed by the Agricultural Biotechnology Research Advisory Committee (ABRAC) Working Group on the Classification of Unmodified Organisms.

(2) Numbers in the body of the table represent the level of safety concern for the unmodified organism on a scale from 1 to 5. Level 1 represents the lowest level of safety concern and Level 5 represents the highest level of safety concern.

TABLE 1 (continued)

Organism	Pest/ pathogen status	Ability to establish	Ecological relationships	Potential for genetic change	Potential for monitoring & control	Overall level of concern
Pseudomonas fluorescens 2-79 (3)	2	2	1	2	1	2
Soybean mosaic virus	3	1	1	2	1	2
Pinus taeda L. (loblolly pine)	1	3	2	2	2	2
Sus spp. (feral pig)	3	3	3	2	3	3
Imported fire ant	5	4	3	4	4	4
Africanized honey bee	4	5	3	4	4	4
Foot and mouth disease virus	5	5	5	5		5

(3) The number "2-79" is part of the strain designation of the organism.

Table 3. REVIEW OF RESEARCH SAFETY PROTOCOLS

Level of safety Concern for the Modified Organism			
Level 1		IBC Approval	N I H G U I D E L I N E S
Level 2		IBC Approval	
Level 3		IBC Approval and USDA Notification	
Level 4		IBC and USDA Approval with ABRAC review	
Level 5			
		Confinement Level	Contained Facilities

Alternative 5

REVIEW OF RESEARCH SAFETY PROTOCOLS

Increasing risk of experiment →

Increasing risk of Organism ↓

Safety Concern Category for Modified Organisms	Laboratory and Contained Experiments	Field Experiments Confinement Levels			
		4	3	2	1
Parent Organism	NA	Exempt	Exempt	Exempt	Exempt
Category 1	IBC Notification or Approval	IBC Notification	IBC Approval	IBC Approval	IBC Approval
Category 2	IBC Notification or Approval	IBC Approval	IBC & USDA	IBC Approval & USDA NOTIF.	IBC & USDA Review & Approval
Category 3	IBC Notification or Approval	IBC Approval & USDA Notification	IBC & USDA Approval ABRAC Review	IBC & USDA Approval ABRAC Review	IBC & USDA Approval ABRAC Review
Category 4	IBC Approval	IBC & USDA Approval ABRAC Review	IBC & USDA Approval ABRAC Review	NYET[c]	NYET
Category 5	IBC Approval	NYET[c]	NYET	NYET	NYET

[a] Practices and procedures assigned, and review requirements stated in NIH Guidelines for Research Involving Recombinant DNA Molecules, and vary with the organism. Containment levels are assigned, and facilities and practices specified in the Guidelines.
Exempt for certain strains of E.coli, yeast, B.subtilis only
IBC Notification for Class 1&2 Microorganisms
IBC Approval for Class 3-5 Microorganisms and for whole plants and animals.

[c] Not yet acceptable for environmentally testing - higher risk

[b] Parent organism may be subject to regulation.

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